MODERN PHARMACOTHERAPY OF CHRONIC HEPATITIS C IN PATIENTS WHO FAILED TO ACHIEVE SUSTAINED VIROLOGIC RESPONSE

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Viral hepatitis is an important problem of modern medical science and practical health care in all countries of the world. Already, the total number of patients with viral hepatitis in the world is 14-15 times higher than the number of HIV-infected people. Viral hepatitis is 50-100 times more contagious than HIV. In recent years there has been a tendency for an increase in cases of chronic forms of the disease. According to WHO experts, about 150 million people suffer from chronic viral hepatitis C (CHC), and 350,000 die annually as a result of liver damage by the hepatitis C virus (HCV) [1]. The incidence and mortality rate due to CHC is progressively increasing on the planet and, according to experts, will double by 2015-2020 [2, 3].

Ukraine is one of the countries with medium prevalence of CHC – about 3% of citizens are infected. In terms of the degree of negative impact on the health of the population and the scale of the incidence of CHC in Ukraine, it is dominant in the structure of infectious pathology, together with influenza and acute infectious diseases of the upper respiratory tract. Nearly 24,786 patients are waiting for treatment in Ukraine [4].

CHC has become a treatable disease with the use of antiviral drugs (> 95%) [5, 6]. To date, for the pharmacotherapy of CHC, a combination of pegylated interferon (PEG-IFN) with Ribavirin and direct-acting antivirals (DAAs) are used. Moreover, most recently, the recommendations of the American Association for the Study of Liver Diseases (AASLD) and the American Society of Infectious Diseases (IDSA) removed the priorities and treatment is now highly recommended for all patients with CHC [7, 8].

Relatively recently, a number of DAAs have been developed for the specific effect on various hepatitis C virus replication sites. These include: NS3/4A protease inhibitors (Boceprevir, Voxilaprevir, Telaprevir, Simeprevir, Grazoprevir, Glecaprevir); NS5B protease inhibitors (Sofosbuvir, Dasabuvir); NS5A protease inhibitors (Ledipasvir, Daclatasvir, Ombitasvir, Elbasvir, Velpatasvir, Pibrentasvir) [9].

To evaluate the effectiveness of treatment, the following criteria are distinguished [10]:

- The answer at the end of treatment means that after the end of HCV treatment, the viral load (VL) is not determined.
- A stable virologic response (SVR) means that the VL became undetectable during treatment and remained undetectable for 12 weeks (SVR-12) or 24 weeks (SVR-24) after treatment. SVR-12 increases the chances of SVR-24, since if the HCV returns, then this usually happen within 12 weeks. SVR -24 is an indicator of cure.
- A quick virologic response (QVR) means that after 4 weeks of treatment, no HCV has been detected in the patient's blood. QVR significantly increases the chances of a successful outcome, but even without a QVR, the patient still has a chance of recovery at the end of the full course.
- An early virologic response (ERV) means that after 12 weeks of treatment, VL decreased by 99% from the level that was before pharmacotherapy.
- Virologic breakthrough: VL became undetectable at one control point of treatment, but later became detectable again. In this situation, a second VN test is needed to ensure that it is detectable. If VL is determined, stop treatment is needed.
- A partial response or lack of a virologic response is characterized by a decrease in VL, but it did not become undetectable after 24 weeks of treatment.
- A zero response is characterized by a slight decrease in VL or the absence of a decrease in VL during treatment.
- Relapse of HCV is considered to be a condition when after the end of treatment HCV is determined in the blood. Approximately 18% of people who have been treated have a relapse. HCV usually appears in the blood 12 weeks after the end of treatment.

Patients who failed to achieve SVR are given a second course of treatment. The decision on this is based on the following main positions: the nature of the previous response, the type of previous therapy and the potential for a new type of treatment, the severity of liver damage, the genotype of the virus and the presence of other prognostic factors and tolerance to previous therapy.

Pharmacotherapy of CHC using a combination of PEG-IFN and ribavirin has a relatively high efficiency, but it depends on the genotype of the HCV. According to the meta-analysis, which included five studies with a total number of patients 20014 patients receiving pharmacotherapy for CHC with a combination of PEG-IFN and ribavirin, SVR comprised 53-73%, depending on the HCV genotype. SVR with EVR was 46-85% also depending on the HCV genotype. SVR without ERV amounted to 10-33% [11]. Therefore, the use of DAAs is a priority in pharmacotherapy of chronic hepatitis C. A number of studies have shown 100% efficacy of CHC pharmacotherapy using 3D therapy based on DAAs (combination of Ombitasvir/Paritaprevir, reinforced by Ritonavir) in combination (Dasabuvir) or a combination of Sofosbuvir, Ledipasvira and INF for 12 weeks [12, 13].

Material & methods

The article analyzes the recommendations of the American Society of Infectious Diseases (IDSA) and the American Association for the Study of Liver Diseases (AASLD), in collaboration with the US International Anti-Virus Society (IAS-USA) [8, 14], as well as the WHO recommendation [15] for repeated pharmacotherapy of CHC in patients who failed to achieve SVR.

Results & discussion

To date, for repeated pharmacotherapy of CHC in patients receiving treatment without achieving a SVR, the following re-treatment regimens are recommended depending on the genotype of the HCV.

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Re-treatment regimens of CHC caused by HCV genotype 1a and 1b in patients treated with PEG-IFN and Ribavirin:

• A daily fixed-dose combination of Elbasvir (50 mg)/Grazoprevir (100 mg) for 12 weeks if patients have not found resistance to protein NS5A for Elbasvir;

• A daily fixed-dose combination of Glacaprevir (300 mg)/Pibrentasvir (120 mg) for 8 weeks;

• A daily fixed-dose combination of Sofosbuvir (400 mg)/Ledipasvir (90 mg) or Velpatasvir (100 mg) for 12 weeks.

The last two regimens are recommended in patients treated with NS3 protease inhibitors (Telaprevir, Boceprevir or Simeprevir) plus PEG-IFN in combination with Ribavirin.

Alternative re-treatment regimens:

• A daily-dose of combination Sofosbuvir (400 mg)/Simeprevir (150 mg) or Daclatasvir (60 mg) for 12 weeks;

• A daily fixed-dose combination of Elbasvir (50 mg)/Grazoprevir (100 mg) with Ribavirin based on body weight for 16 weeks, if patients have not found substitutions associated with resistance to protein NS5A for Elbasvir. In the case of a high level of resistance to the NS5A protease inhibitor for Elbasvir, it is necessary to extend the course of treatment up to 16 weeks.

Re-treatment regimens for CHC caused by HCV genotype 1 in patients treated with Sofosbuvir but not treated with NS5A protease inhibitors:

• A daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg)/Voxilaprevir (100 mg) for 12 weeks for patients with genotype 1a;

• A daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg) or 12 weeks for patients with genotype 1b;

• A daily fixed-dose of the combination of Glacaprevir (300 mg)/Pibrentasvir (120 mg) for 12 weeks, regardless of the HCV subtype (1a or 1b).

Alternative re-treatment regimen is a daily fixed-dose of the combination of Ledipasvir (90 mg)/Sofosbuvir (400 mg) in combination with Ribavirin based on body weight, with the exception of cases of treatment failure with Simeprevir, for 12 weeks.

Recommended re-treatment regimens for CHC caused by HCV genotype 2:

• A daily fixed-dose combination of Glacaprevir (300 mg)/Pibrentasvir (120 mg) for 8 weeks;

• A daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg) for 12 weeks.

Alternative treatment regimen is a daily dose of combination Daclatasvir (60 mg) and Sofosbuvir (400 mg) for 12 weeks.

Recommended re-treatment regimen for CHC caused by HCV genotype is a daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg) for 12 weeks.

Alternative re-treatment regimens:

•A daily dose of Daclatasvir (60 mg) in combination with Sofosbuvir (400 mg) for 12 weeks;

• A daily fixed-dose combination of Glacaprevir (300 mg)/Pibrentasvir (120 mg) for 16 weeks;

• A daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg)/Voxilaprevir (100 mg) for 12 weeks when there is a mutation of the NS5A Y93H gene when determining resistance to NS5A protease inhibitors.

Recommended re-treatment regimens for CHC caused by HCV genotype 4:

• A daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg) or Ledipasvir (90 mg) for 12 weeks;

• A daily fixed-dose combination of Glacaprevir (300 mg)/Pibrentasvir (120 mg) for 8 weeks;

• A daily fixed-dose combination of Elbasvir (50 mg)/Grazoprevir (100 mg) for 12 weeks for patients who have had a virologic relapse after previous treatment combination PEG-IFN/Ribavirin.

Alternative re-treatment regimens:

•A daily fixed-dose combination of Paritaprevir (150 mg)/Ritonavir (100 mg)/Ombitasvir (25 mg) and Ribavirin based on weight for 12 weeks;

• A daily fixed-dose combination of Elbasvir (50 mg)/Grazoprevir (100 mg) and Ribavirin based on body weight for 16 weeks.

Recommended re-treatment regimens for CHC caused by HCV genotype 5-6 in patients treated with PEG-IFN in combination with Ribavirin:

• A daily fixed-dose combination of Glycaprevir (300 mg)/Pibrentasvir (120 mg) for 8 weeks;

• A daily fixed-dose combination Ledipasvir (90 mg)/Sofosbuvir (400 mg) for 12 weeks;

• A daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg) for 12 weeks.

Recommended re-treatment regimen for CHC caused by HCV genotype 5-6 in patients treated with DAAs (including drugs that are NS5A protease inhibitors):

• A daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg)/Voxilaprevir (100 mg) for 12 weeks.

An important problem during pharmacotherapy of patients with CHC is resistance to antiviral therapy. The amino acid polymorphism of NS3, NS5A and NS5B viral proteins in different HCV genotypes and subtypes, as well as the same strains of genotypes and subtypes that reduce DAAs efficacy, is referred to as resistance-related variants (RRV). However, antiviral therapy fails only when RRV is combined with other factors and features of the patient's body, decreased sensitivity to antiviral therapy, or insufficient duration of therapy [12, 16, 17]. As seen in the recommendations for recurrent CHC pharmacotherapy, possible resistance to the protease inhibitor NS5A for Elbasvir, as well as to the NS3 protease inhibitors for Telaprevir, Boceprevir, or Simeprevir was considered.

The results obtained from published sources indicate that current strategies for recurrent pharmacotherapy of CHC patients in most cases of unsuccessful pre-treatment allow the achievement of SVR using DAAs during re-treatment, including those regimens that have efficacy in resistance-associated variants.

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Modern pharmacotherapy of chronic hepatitis C in patients who failed to achieve sustained virologic response

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Introduction. According to WHO experts, about 150 million people suffer from chronic viral hepatitis C (CHC), and 350,000 die annually as a result of liver damage by the hepatitis C virus (HCV). Ukraine is one of the countries with medium prevalence of CHC – about 3% of citizens are infected. CHC has become a treatable disease with the use of antiviral drugs (> 95%). To date, for the pharmacotherapy of CHC, a combination of pegylated interferon (PEG-IFN) with ribavirin and direct-acting antivirals (DAAs) are used. Pharmacotherapy of CHC using a combination of PEG-IFN and ribavirin has a relatively high efficiency, but it depends on the genotype of the HCV. Therefore, the use of DAAs is a priority in pharmacotherapy of chronic hepatitis C. Patients who failed to achieve sustained virologic response (SVR) are given a second course of treatment (retreatment). The decision on this is based on the following main positions: the nature of the previous response, the type of previous therapy and the potential for a new type of treatment, the severity of liver damage, the genotype of the virus and the presence of other prognostic factors and tolerance to previous therapy. **Material & methods.** The article analyzes the recommendations of the American Society of Infectious Diseases (IDSA) and the American Association for the Study of Liver Diseases (AASLD), in collaboration with the US International Anti-Virus Society (IAS-USA), as well as the WHO recommendation for repeated pharmacotherapy of CHC in patients who failed to achieve SVR. **Results & discussion.** To date, for re-treatment of CHC in patients receiving treatment without achieving a SVR, the different re-treatment regimens are recommended depending on the genotype of the HCV. An important problem during pharmacotherapy of patients with CHC is resistance to antiviral therapy. The amino acid polymorphism of NS3, NS5A and NS5B viral proteins in different HCV genotypes and subtypes, as well as the same strains of genotypes and subtypes that reduce DAAs efficacy, is referred to as resistance-related variants (RRV). However, antiviral therapy fails only when RRV is combined with other factors and features of the patient's body, decreased sensitivity to antiviral therapy, or insufficient duration of therapy. As seen in the recommendations for recurrent CHC pharmacotherapy, possible resistance to the protease inhibitor NS5A and to the NS3 protease inhibitors was considered. **Conclusion. The** results obtained from published sources indicate that current strategies for recurrent pharmacotherapy of CHC patients in most cases of unsuccessful pre-treatment allow the achievement of SVR using DAAs during re-treatment, including those regimens that have efficacy in resistance-associated variants.

Key words: chronic viral hepatitis C, re-treatment, sustained virologic response.

References

1. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. // Lancet Gastroenterol Hepatol. 2017. May. Vol. 2. N. 5. P. 325-336.
2. Gower E, Estes C, Blach S , Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. // J Hepatol. 2014. N.61(1Suppl). P. 45-57.
3. Centers for Disease Control and Prevention. Viral hepatitis: surveillance for viral hepatitis – United States, 2015.
4. MOZ Ukrayiny. Hepatyt C - bil′she ne vyrok: v Ukrayini vylikuyut′ usyu cherhu patsiyentiv.
5. World Health Organization. Hepatitis C: fact sheet.
6. World Health Organization. Hepatitis C.
7. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. // Clin Infect Dis. 2014 Sep 15. Vol.59 N. 6. P. 765-773.
8. American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. // Hepatology. 2015 Sep. Vol. 62. N. 3. P. 932-54.
9. Shahid I, AlMalki WH, Hassan S, Hafeez MH. Real-world challenges for hepatitis C virus medications: a critical overview. // Crit Rev Microbiol. 2018 Mar. Vol. 44. N. 2. P. 143-160.
10. Viral hepatitis C. Adapted evidence-based clinical guideline (updated) URL: https://dec.gov.ua/wp-content/uploads/images/dodatki/2016_729_VGC/2016_729_AKN_VGC.pdf
11. Brittany E. Yee, Derek Lin, Nghia H. Nguyen, Bing Zhang, Philip Vutien, Carrie R. Wong, Glen A. Lutchma, Mindie H. Nguyen Higher sustained virologic response (SVR) in patients with early virologic response (EVR) and hepatitis C genotype 4 (HCV-4) compared to genotype 1 (HCV-1) with pegylated interferon and ribavirin (PEG IFN+RBV): a comparative analysis from a meta-analysis// Hepatology. 2014. №4 (60). p.690-691.
12. Shostakovich-Koretska LR, Shevchenko-Makarenko OP, Timofeeva LV, Tkachenko VD Problematic issues of the effectiveness of treatment of patients with chronic viral hepatitis C according to the State program and ways to solve them// Medical prospects. 2018. No. 3. T.XXII. with. 84-92.
13. Pronyuk KyU, Golubovskaya OA, Skurba AV The effectiveness of the combination of ledipasvir / sofosbuvir in the treatment of chronic hepatitis C: an analysis of clinical trials and our own experience // Clinical infectology and parasitology. 2018. № 1. T. 7. c. 76-83.
14. Expanding access to effective hepatitis C treatment through community-based treatment models for vulnerable populations in Ukraine's limited resources URL: http://aph.org.ua/uk/nasha-robota/ukraine/rozshyrennya-dostupu-do-efektyvnogo-likuvannya-gepatytu-s-cherez-

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modeli-likuvannya-na-rivni-gromad-dlya-urazlyvyh-grup-naselennya-v-umovah-obmezhenyh-resursiv-ukrayiny/
15. World Health Organization. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva, Switzerland: World Health Organization.
16. AASLD/IDSA HCV Guidance: Recommendations for testing, managing, and treating hepatitis C [Internet]. American Association for the Study of Liver Diseases (AASLD). 2018; 265..
17. Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection // Gastroenterol. 2014. Vol. 147. №2. c. 359-365.

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